

REMARKS

This is in response to the Office Action of March 4, 2009. Claims 1-7 are pending in the application. Claim 1 is amended – without change of scope – to clarify the processing steps involved in the biological transformation method being claimed. This is a non-narrowing amendment. No new matter is introduced by this Amendment, and no new issues are raised thereby. Entry of this Amendment in order to place the application into condition for allowance, or into better condition for appeal, is earnestly solicited.

Rejection on the ground of obviousness-type double patenting

Claims 1, 3, and 5 were provisionally rejected on the ground of obviousness-type double patenting, over claims 1 and 24 of co-pending application Serial No. 11/213,962. Office Action, pages 2-4. The rejection is respectfully traversed.

Claim 1 in SN 11/213,962 is a compound claim. None of present claims 1, 3, or 5 are compound claims. There is no double patenting of any of claims 1 or 3 (process) or 5 (culture) with respect to claim 1 (compound) of the reference application.

Claim 24 in SN 11/213,962 claims a production process. Claim 5 herein claims a culture of a microorganism. There is no double patenting of claim 5 (culture) with respect to claim 24 (process) of the reference application.

Claim 24 of SN 11/213,962 broadly recites culturing a specified microorganism in a nutrient medium, collecting a complex compound from a culture solution, “and carrying out various modification synthesis by using the obtained compounds as a starting material to obtain derivatives thereof.” It is respectfully submitted that the presently claimed process of providing a specific complex compound, mixing that compound with a microorganism, incubating the mixture, and collecting a specific different complex compound from the incubated solution – is not an obvious variation of “carrying out various modification synthesis.” In Applicants’ process, a specific complex compound – formula (I) – is transformed into another, different complex compound – formula (II). In reference process claim 24, no such biological transformation of one specific complex compound into another specific complex compound by a microorganism is recited.

As discussed in the interview between Examiner Shahnan Shah and Applicants' representative, Richard Gallagher, on November 10, 2008, it is well known for those of skill in the art that fermentation as disclosed in SN 11/213,962 and bioconversion or biotransformation employed by the present invention were separately discovered in the history and recognized as significantly different processes.

For example, "Industrial Biotransformations," Andreas Liese et al., Wiley-VCH, 2000, states as follows in the section headed "2 History of Industrial Biotransformations – Dreams and Realities" (copy enclosed):

In the course of time, it was discovered that microorganisms could modify certain compounds by simple, chemically well-defined reactions which were further catalyzed by enzymes. Nowadays, these processes are called "biotransformations." The essential difference between fermentation and biotransformation is that there are several catalytic steps between substrate and product in fermentation while there are only one or two in biotransformation. The distinction is also in the fact that the chemical structures of the substrate and the product resemble one another in a biotransformation, but not necessarily in a fermentation.

This reference and the state of the art teach away from the claimed invention that employs a bioconversion step to make 11107D from 11107B.

Accordingly, withdrawal of the double patenting rejection is in order and is earnestly solicited.

Rejection under 35 U.S.C. § 102(b)

Claims 1, 3, and 5 were rejected under 35 U.S.C. § 102(b) as being anticipated by Mizui et al., WO 02/060890-A1 ("Mizui"). Office Action, pages 4-6. The US equivalent specification – Publication No. 2006/0079572, Serial No. 11/213,962 – is a divisional application of Serial No. 10/470,806 (issued as U.S. Patent No. 7,026,352). The references to Mizui below refer to the U.S. publication equivalent of the Mizui reference. The rejection is respectfully traversed.

Mizui shows obtaining both 11107B and 11107D biologically from a starting nutrient medium. The reference fails to show 11107B used as a starting material and also fails to show 11107B being hydroxylated at the 16-position by means of a microorganism. In other words, Mizui shows

nutrient medium → 11107B, 11107D

while the present invention, in contrast, requires

11107B → 11107D.

That is – while Mizui et al. may disclose 11107B and 11107D – Mizui et al. do not disclose how to synthesize 11107D from 11107B using a bacteria, as required by Applicants' claims.

The Examiner contends at the middle of page 6 of the Office Action that Applicants' "claims are drawn to a product by a process." This is incorrect. Claims 1 and 3 are drawn to a process of providing a specific complex compound, mixing that compound with a microorganism, incubating the mixture, and collecting a specific different complex compound from the incubated solution. Claim 5 is drawn to a culture of a particular strain of *Streptomyces*. None of claims 1, 3, or 5 is drawn to a product by process.

The Examiner's contention goes on to allege that Mizui et al. do disclose a method of producing macrolide 11107D by incubating a bacterial strain with the macrolide 11107B because its paragraph [0274] recites "the present invention provides the production process of the compound of the present invention, **a pharmacologically acceptable salt thereof or hydrate of** them, which comprises culturing *Streptomyces* sp. Mer. 11107, FERM P-18144 or its variant in a nutrient culture medium, collecting the compounds described in any of the above are from the culture solution, and **carrying out various modification synthesis by using the obtained compounds as a starting material to obtain derivatives thereof.**" (Emphasis in original.)

Applicants respectfully disagree. As pointed out above, the Mizui reference neither specifically describes a method of producing 11107D from 11107B, nor such production by bioconversion, both of which are employed in the present invention. The Mizui reference discloses the process only generally, as "various modification synthesis by using the obtained compounds as a starting material to obtain derivatives thereof." (Emphasis added.)

The Examiner contends at the bottom of page 5 of the Office Action that "Asai et al. (Mizui et al.) teach ... conversion of 111107B (*sic*) to 1107D (*sic*) biological transformation or bioconversion (*see abstract*) Since FERM BP-8551 strain characteristics is unknown, the strain has not been disclosed. Therefore it is determined that the strain of *Streptomyces* used by

Asai et al. is identical to the strain recited in claim 5 since the required bioconversion is achieved by the strain of Asai et al. The prior art teaches the claimed invention.”

Applicants would first like to address the fact that the Examiner’s assertion in the first sentence is not factually supported. The Examiner is respectfully invited to review Asai et al. (Mizui et al.) to confirm that it does not disclose the conversion of 11107B to 11107D biological transformation or bioconversion in its abstract or any other parts.

Secondly, Applicants respectfully submit that the present application does disclose the characteristics of FERM BP-8551 strain. The taxonomical properties of the AB-1704 strain (i.e. FERM BP-8551. *See*, bridging paragraph, pages 5-6 of the specification) are fully described in pages 11-13 of the specification. These properties are apparently different from those of Mer-11107, the *Streptomyces* used by Asai et al., as disclosed in paragraphs [0296] - [0317] of US 2006/0079572. For example, morphology of aerial hyphae of FERM BP-8551 is “rectiflexibles” whereas aerial hyphae of Mer-11107 is “spirales.”

Withdrawal of the rejection of claims 1, 3, and 5 under 35 U.S.C. § 102(b) as being anticipated by Mizui in order and is earnestly solicited.

Translation of priority document

At the top of page 5 of the Office Action, the Examiner indicates that Applicants had not filed a translation of their priority document. Accordingly, Applicants enclose herewith a translation into the English language of a certified copy of their priority application, along with a statement from the translator attesting to the accuracy of the translation.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 3 and 5 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Seki-Asano et al., *J. Antibiotics*, 47(12):1395-1401, 1994 (hereinafter, “Seki-Asano”). Office Action, pages 6-9. The rejection is respectfully traversed.

The Examiner states at the bottom of page 7 of the Office Action: “Since FERM BP-8551 strain characteristics is unknown, the strain has not been disclosed. Therefore it is determined that the strain of *Streptomyces* used by Seki-Asano et al. is identical to the strain recited in claim

5 since the required bioconversion is achieved by the strain of Seki-Asano et al.” Applicants respectfully disagree. As noted above, the taxonomical properties of FERM BP-8551 are fully described in pages 11-13 of the specification. These properties are manifestly different from those of A-9561, the *Streptomyces* used by Seki-Asano et al., as disclosed in Tables 1 and 2.

At the top of page 8 of the Office Action, Examiner concludes that “[i]t would be *prima facie* obvious to one of the ordinarily skilled in the art to replace the methyl group at the position 16 of the FD-895 to a hydroxyl group to obtain compound 11107D of formula II.” At the bottom of this page, the Examiner further argues that “motivation for hydroxylation of 11107B at position 16 is provided by one of the ordinarily skilled in the art to replace methyl group at the position 16 of the FD-895 to a hydroxyl group to obtain compound 11107D.”

Applicants respectfully disagree in two respects. Firstly, Macrolide 11107D in the present invention and FD-895 in Seki-Asano are different from each other more significantly than the Examiner assumes. FD-895 differs from 11107D in having no hydroxyl group at the 16-position. In this regard, the Office Action is factually incorrect in that it states “to replace the methyl group at the position the position 16 of the FD-895 to a hydroxyl group to obtain compound 11107D of formula II.” (emphasis added.) since there is a methyl group at the position 16 of both FD-895 and 11107D. It should be noted that FD-895 is also different from 11107B and 11107D, having a hydroxyl group in the 17-position and having a methoxy group in the 21-position.

Secondly, the Seki-Asano reference provides no teaching relevant to biological hydroxylation of a particular compound at a particular position. Seki-Asano merely discloses isolation of a macrolide, which differs significantly in structure from the claimed 11107D macrolide, from the spent media of a culture of *Streptomyces hygroscopicus* A-9561. The Seki-Asano reference fails to show 11107B used as a starting material and also fails to show a microorganism being used to hydroxylate a particular compound at a particular position (much less, 11107B at the 16-position) and also fails to show 11107D being obtained as a final product. Seki-Asano fails to suggest that *Streptomyces hygroscopicus* A-9561 can be used to bioconvert 11107B to 11107D by hydroxylation at the 16-position. Therefore, no motivation or rationale

for hydroxylation of 11107B at position 16 is provided by the Seki-Asano reference in particular or by the prior art in general.

In the sentence bridging pages 8-9 of the Office Action, the Examiner contends that “substitution of methyl or hydroxyl group in the same scaffold in a family of known antibiotic compounds is considered as optimization of assay parameters and will be well within reach of one skilled in the art.” Applicants respectfully submit that being “within reach” is not a proper standard for an obviousness rejection. In fact, hydroxylation of a compound with complex chemical structure like 11107B at specific position by using a conventional chemical synthesis method is highly difficult. As described at the top of page 2 of the specification, the inventors of the present invention have made a trial to select microorganism capable of transforming the 16-position hydrogen atom hydroxyl group of 11107B by screening from wide range of microorganism groups, and finally found the strains claimed. What the Examiner appears to be saying in this analysis is that the present invention is obvious because a person of ordinary skill in the art could carry it out. “The mere fact that a reference could be modified to produce the patented invention would not make the modification obvious unless it is suggested by the prior art.” *Libbey-Owens Ford Co. v. BOC Group Inc.*, 655 F. Supp. 897, 906, 4 USPQ2d 1097, 1103 (D.N.J. 1987) (emphasis supplied). “Something in the prior art as a whole must suggest the desirability ... of making the combination.” *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051-52, 5 USPQ2d 1434, 1438 (Fed. Cir. 1988) (emphasis supplied).

Withdrawal of the rejection of claims 1, 3, and 5 under 35 U.S.C. § 103(a) as being unpatentable over the Seki-Asano reference is in order and is earnestly solicited.

CONCLUSION

If the Examiner has any questions or comments, please contact Richard Gallagher, Registration No. 28,781, at the offices of Birch, Stewart, Kolasch & Birch, LLP. Mr. Gallagher can be reached at (703) 205-8008.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for

any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

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Respectfully submitted,

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